



Serial Number: 09/528,989
Attorney Docket Number: 9676-292

REMARKS

Claims 1-51, as amended, are currently pending in the above-captioned application for the Examiner's review and consideration. Claim 34 has been amended to correctly recite its dependency on claim 33, where the proper antecedent basis for "the salt" is found. Claim 47 was amended to more clearly recite the invention. As no new matter is added by these amendments, Applicants respectfully request their entry into the record of this application at this time.

Initially, Applicants note that claims 1-51 stand rejected on page 1 of the Office Action, but claim 51 is not indicated as being rejected anywhere else in the Office Action, particularly not in the double patenting rejection and the second obviousness rejection that otherwise include claims 1-50. Applicants have treated this as an inadvertent error and have replied as if claim 51 was included in these rejections. In addition, in the other anticipation and obviousness rejections where the claim ranges are terminated at 50, Applicants have also replied as if claim 51 was included in the rejections.

A Brief Description of the Claimed Invention

The present invention relates to an injectable composition suitable for tissue bulking that comprises biocompatible, swellable, hydrophilic, non-toxic and substantially spherical microspheres and a biocompatible carrier. The claimed invention further requires that the composition be injectable through needles of about 18 to 26 gauge and that the microspheres swell to a predetermined size after injection. The invention also relates to a method of tissue bulking and a kit for performing tissue bulking that comprise the microspheres.

As stated in the specification, different materials, such as carbon particles, silicone particles, TEFLON paste, and collagen beads have been used for tissue bulking, such as for the treatment of gastro-esophageal reflux disease (GERD) and urinary incontinence, all with disappointing results. *See, e.g.*, Specification at page 5 line 9 to page 6, line 18. To the contrary, the present invention claims an injectable composition that comprises hydrophilic, swellable and spherical microspheres, which have never been used for tissue bulking

purposes as presently claimed. Further, the present invention claims a method of tissue bulking that comprises injecting the microspheres through a needle of about 18 to 26 gauge. In addition, the invention claims a kit for performing tissue bulking that comprises an 18 to 26 gauge needle, means for injection, and the microspheres that are also both injectable through the needle and not capable of being eliminated through macrophage or other elements of the immune system.

Therefore, not only does the present invention relate to a specific type of microspheres that have never been used for tissue bulking purposes as presently claimed, but the invention also claims different ways of employing the unique microspheres in tissue bulking purposes, such as injectable composition, method of treatment and kit.

Provisional Double Patenting Rejection Should Be Withdrawn

Claims 1-51 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of co-pending U.S. Patent Application Nos. 09/528,990 ("the '990 application") and 09/263,773 ("the '773 application") for the reasons set forth on page 2 of the Office Action. Applicants respectfully traverse this rejection for the following reasons.

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The claims of the '990 application, as they currently stand, involve an injectable composition, and a method of dermal augmentation comprising same, wherein the composition is injectable through needles of about 30 gauge or smaller. On the contrary, the instant claims, as amended, recite an injectable composition, and a method of tissue bulking comprising same, wherein the composition is injectable through needles of about 18 to 26 gauge. As defined in the instant specification, tissue bulking refers to *non-dermal* tissues (See, Specification at page 11, lines 12-17), thus expressly excluding the subject matter of the '990 application, which relates to *dermal tissue, i.e., the skin and related areas*. In addition, one of ordinary skill in the art knows that the diameter of needles of about 18 to 26 gauge is larger than that of needles of about 30 gauge or smaller and, therefore, materials (e.g., microspheres) that could fit through needles of about 18 to 26 gauge is larger than that which could fit through needles of about 30 gauge or smaller.

In view of these distinctions, Applicants respectfully submit that it would not have been obvious to one of ordinary skill in the art, based on different compositions used for different purposes as disclosed in the '990 application, to achieve the present invention. Further, claims 21-46 recite methods of tissue, including methods for injection into specific areas of the body and for treatment of specific diseases, none of which is suggested by the '990 application. As such, even if the claims of the '990 application were to be allowed, Applicants respectfully submit that the presently claimed invention is patentably distinct from that of the '990 application.

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The claims of the '773 application, as they currently stand, involve methods of treatment for urinary incontinence, urinary reflux disease, and gastro-esophageal reflux disease, not compositions, methods, or kits for tissue bulking, as recited in the instant claims. As these inventions are patentably distinct, it would not have been obvious to one of ordinary skill in the art, based on the disclosure of the '773 application, to achieve the presently claimed invention. Therefore, even if the claims of the '773 application were to be allowed as currently pending, Applicants respectfully submit that they are drawn to a patentably distinct invention form that of the instant claims, as amended.

For the forgoing reasons, Applicants respectfully submit that the provisional non-statutory obviousness-type double patenting rejections have been overcome and respectfully request their reconsideration and withdrawal.

Rejection under 35 U.S.C. § 112 Should Be Withdrawn

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Claim 34 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons set forth on pages 2-3 of the Office Action. Applicants have amended claim 34 to depend from claim 33, instead of from claim 22, to provide antecedent basis for the phrase "the salt." Thus, Applicants respectfully submit that the indefiniteness rejection has become moot and should be withdrawn.

Rejections Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1-4, 6-8, 13, 21-22, 26, 31-33, 38, and 45-51 were rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,550,187 to Rhee et al. ("Rhee") for the reasons set forth on page 3 of the Office Action. Applicants respectfully traverse this rejection.

Rhee discloses a method for preparing crosslinked biomaterial compositions for use in tissue augmentation and a method for effecting tissue augmentation. Both methods require mixing a biocompatible polymer with a dry crosslinking agent to *initiate* crosslinking between the polymer and the agent and delivering the mixture into either a mold or the tissue site in need of augmentation. *See, e.g.*, Rhee at col. 4, lines 2-21. Rhee also discloses a kit for tissue augmentation which requires three syringes and one or more needles to facilitate the above-mentioned mixing of dry crosslinking agent and biocompatible polymer. *Id.* at col. 15, lines 26-34.

Rhee, however, does not disclose a composition, method, or kit for tissue bulking that comprises biocompatible, swellable, hydrophilic, non-toxic and substantially spherical microspheres, as recited in independent claims 1, 21, and 47 of the present application. In fact, Rhee's methods only relate to initiating the crosslinking between the dry crosslinking agent and the biocompatible material just prior to their injection into a mold or the body, see, e.g., Rhee at col. 4, lines 2-21, and require that the mixture must be extruded from the syringe before complete crosslinking has occurred between the biocompatible polymer and the crosslinking agent. *Id.* at col. 15, lines 8-10. The disclosure of Rhee is silent as to any aspect of either a microsphere or a swelling material as an injectable material, as recited in the present invention.

To anticipate, under 35 U.S.C. § 102, a prior art reference must disclose every element of the claimed invention. *See, e.g.*, In re Bond, 910 F.2d 831, 837 (Fed. Cir. 1991). Rhee fails to anticipate any of claims 1-4, 6-8, 13, 21-22, 26, 31-33, 38, and 45-51, because, as shown above, Rhee does not disclose every element of any of the claims. Therefore, the rejection under 35 U.S.C. § 102(b) in view of Rhee must be withdrawn.

Claims 1-4, 6-8, 13, 21-22, 26, 31-33, 38-39, and 42-46 were rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,922,025 to Hubbard ("Hubbard") for the reasons set forth on pages 3-4 of the Office Action. Applicants respectfully traverse this rejection.

Hubbard discloses an augmentation material comprising smooth rounded, substantially spherical, particles of a finely divided *ceramic* material that is substantially non-resorbable. *See* Hubbard at col. 5, lines 1-3 and lines 36-37. Hubbard also discloses a method for preparing dense, rounded or substantially spherical *ceramic* particles such as calcium hydroxyapatite by spray-drying a slurry of submicron particle size material; optionally presintering at about 800°C to 1000°C; optionally agitating or rolling the globular particles; and sintering the particles in a crucible at temperatures of about 1050°C to 1200°C. *Id.* at col. 5, line 53 through col. 6, line 16.

Hubbard, however, does not disclose a composition, method, or kit for dermal augmentation that comprises biocompatible, swellable, hydrophilic, non-toxic and substantially spherical microspheres, as recited in independent claims 1, 22, and 48 of the present application. Hubbard further fails to disclose or suggest a composition that comprises microspheres that swell to a predetermined size after injection, much less microspheres that swell after injection up to four times their pre-injection size, as presently claimed. In fact, the finely divided ceramic particles disclosed in Hubbard are, by definition, the direct opposite of the *swellable and hydrophilic* characters of the microspheres required by the present invention. Further, the preferred microspheres of the instant invention comprise crosslinked polymers or copolymers, not calcium hydroxyapatite, nor any ceramic disclosed in Hubbard. (See, e.g., claims 12 and 25).

Since Hubbard fails to disclose every element of any of claims 1-4, 6-8, 13, 21-22, 26, 31-33, 38-39, and 42-46, Hubbard does not anticipate any of the claims. *See, e.g., In re Bond*, 910 F.2d 831, 837 (Fed. Cir. 1991). Thus, Applicants respectfully request that this anticipation rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 1-13, 17-18, 21-26, and 31-51 were rejected by the Examiner under 35 U.S.C. § 103(a) as being obvious over Hubbard or Rhee, in view of U.S. Patent No. 5,648,100 to Boschetti *et al.* ("Boschetti") and Japanese Patent No. JP 06-056676 to Shinichi Hori ("Hori") for the reasons set forth on pages 4-6 of the Office Action. Applicants respectfully traverse this rejection.

The Examiner has conceded that both Rhee and Hubbard fail to teach emulsions, contrast agents, acylamino-e-propion-amido-3-triiodo-2, 4, 6-benzoic acid, preferred embodiments of the microspheres, therapeutic agents, radiopacifying agents, and contrast media. The Examiner has also conceded that Hubbard fails to teach a kit. As Applicants have noted herein, both Rhee and Hubbard also fail to disclose or suggest a composition, or a method or kit using a composition comprising microspheres that are swellable upon injection, as recited in the instant claims.

In addition to lacking key features of the instant claims, Rhee and Hubbard both actually teach one of ordinary skill in the art away from the claimed invention. Rhee discloses a method of preparing crosslinked biomaterial compositions that is "user-friendly" to the physician because the method provides *in situ* crosslinking biocompatible polymers with dry crosslinking agent. *See, e.g.*, Rhee at col. 3, line 65 - col. 4, line 21. According to Rhee, the mixture of the biocompatible polymer and the dry crosslinking agent is either extruded into a mold to form implants of desired shape and size or injected, after initiation of crosslinking, into the tissue. *See, e.g.*, Rhee at col. 3, line 65 - col. 4, line 21 and col. 14, line 53 - col. 15, line 64. Furthermore, Rhee requires that the mixture must be extruded from the syringe before complete crosslinking has occurred between the biocompatible polymer and the crosslinking agent. *Id.* at col. 15, lines 8-10. Thus, what Rhee discloses is a method in which no solid implant material, not to mention the specific microspheres claimed in the present invention, is present in the composition. Therefore, a person of ordinary skill in the art, based on Rhee's disclosure, would be taught away from the present invention, which recites compositions, methods and kits that require microspheres that are already polymerized.

Hubbard, too, teaches one of ordinary skill in the art away from the claimed invention, which requires swellable hydrophilic microspheres, by its disclosure of a biocompatible composition made from ceramic particles of calcium hydroxyapatite or calcium phosphate-based or alumina-based materials (*see* Hubbard at col. 5, lines 46-52; col. 7, lines 27-36) and a method of soft tissue augmentation comprising forming such ceramic particles by spray-drying, presintering and/or sintering at extremely high temperatures, and agitating or rolling the globular particles (*id.* at col. 5, line 53 through col. 6, line 16).

Boschetti, nevertheless, fails to remedy the deficiencies of Rhee or Hubbard in that it does not disclose or suggest a composition that comprises microspheres that swell to a predetermined size after injection. Thus, alone or in any combination with Rhee and/or Hubbard, Boschetti fails to disclose or suggest all the instantly claimed elements.

Further, Boschetti actually teaches away from the claimed invention through its disclosure that the microspheres be used as emboli for therapeutic vascular occlusion (*see* Boschetti at col. 1, lines 10-25), as opposed to their use in tissue bulking, as presently claimed. Contrary to the Examiner's indication on page 5 of the Office Action, Applicants have found no disclosure or suggestion of a method of tissue bulking in the entire Boschetti reference. The only reference Applicants have found to "tissue" in Boschetti is found at col. 7, line 28, and appears in reference to the controllability of effects of the embolic microspheres on tissue surrounding an occlusion when the particle distribution is narrow. *See* Example 20. Applicants note that Boschetti teaches that its microspheres afford a 100% occlusion of the vascular lumen and that control of "the distance of the occlusion" is possible through calibration, as well as a wide range of microsphere diameters (about 10 to about 2000 microns). *Id.* at col. 1, lines 51-61. Applicants submit, however, that control over the diameter of a microsphere does not obviate control over the diameter of a swollen microsphere after injection, especially without reference to swelling of any kind.

Hori, like Boschetti, teaches away from the claimed invention through its disclosure that granules of a water-absorbing resin be used as emboli in occlusions or embolizations in blood vessels (*see* Hori Abstract). There is no disclosure or suggestion in Hori that microspheres, as recited in the present invention, being used for tissue bulking.

Furthermore, one of ordinary skill in the art would not have had a motivation to combine the Hori and Boschetti references with Rhee and/or Hubbard. Hori and Boschetti both involve compositions for emboli in blood vessels, whereas the disclosures of Rhee and Hubbard involve tissue augmentation. Applicants maintain that one of ordinary skill in the art would not have considered their disclosures relevant enough to each other to combine them. Applicants respectfully submit that the only impetus for combining these references in such a way is contained in the instant specification; and that, of course, is a classic case of hindsight.

Applicants also submit that one of ordinary skill in the art, even if somehow motivated to combine these disparate prior art references, would nevertheless have had no reasonable expectation of success in achieving the claimed invention. In order to achieve the claimed invention, the water-absorbing ability of the Hori composition would have to have been combined with the hydrophilic character and the ability to form a sterile particulate suspension without aggregates, as taught by Boschetti. That combination being difficult to achieve in and of itself, one of ordinary skill in the art would have also had to introduce the biocompatibility, non-toxicity, and substantially spherical nature of the ceramic particles of Hubbard to the emboli of Boschetti and Hori, which are disclosed for a totally different application.

For any of the foregoing reasons, Applicants submit that a *prima facie* case of obviousness has not been made and, in any event, cannot be maintained. Applicants therefore respectfully request that this obviousness rejection be reconsidered and withdrawn.

Claims 1-51 were rejected under 35 U.S.C. § 103(a) as being obvious over Rhee or Hubbard, in view of Boschetti and Hori, further in view of U.S. Patent No. 5,855,610 to Vacanti *et al.* ("Vacanti") for the reasons set forth on pages 6-7 of the Office Action. Applicants respectfully traverse this rejection.

Although the Examiner notes that Vacanti teaches the use of autologous cells seeded in a fibrous matrix, Applicants submit that this disclosure does not remedy the deficiencies of the other cited prior art references. Vacanti discloses a cell-matrix structure

that, after implantation into certain tissue, results in improved yields of engineered tissue. Applicants submit that the combination of these five references is even more disparate, reducing even further any possible motivation of one of ordinary skill in the art to combine the Vacanti disclosure, being drawn to tissue engineering and cell regrowth, the disclosures of Rhee, relating to *in situ* crosslinking of biocompatible polymers, Hubbard, involving tissue augmentation through ceramic microspheres, and Hori and Boschetti, which relate to therapeutic occlusions of blood vessels. Further, there is even less reasonable expectation of one of ordinary skill in the art to succeed in achieving the claimed invention because of the disparate references.

For any of the foregoing reasons, Applicants submit that a *prima facie* case of obviousness has not been made and, in any event, cannot be maintained. Applicants therefore respectfully request that this obviousness rejection be reconsidered and withdrawn.



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Conclusions

Applicants respectfully submit that all double patenting, anticipation, and obviousness rejections have been overcome and that the claims, as amended, are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicants respectfully request a personal or telephonic interview to discuss any remaining issues and to expedite the eventual allowance of this application.

No fee, except for the Petition for Extension of Time submitted herein, is believed to be due for this submission. Should any additional fee be required, however, please charge the required fee to Pennie & Edmonds Deposit Account No. 16-1150.

Respectfully submitted,

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Enclosures